

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT:	Gao et al.)	GROUP ART UNIT:	1615
SERIAL NO.:	09/451,641)	CONFIRMATION NO.:	9327
EXAMINER:	Tran)	ATTORNEY DOCKET	3169/1/US
FILED:	November 30, 1999)	NO.:	(PC010664)
TITLE:	CELECOXIB COMPOSITIONS			

Commissioner for Patents
P.O. Box 1450
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RESPONSE TO OFFICE ACTION

Sir:

In response to the Office action of January 13, 2006, the time for response to which has been extended by three months, please consider the following remarks.

Claims 1-10, 12-50, 72-75, 84, and 86-90 are currently pending. Claims 1, 2, 4-10, 12-50, 72-75, 84, and 86-90 stand rejected under 35 U.S.C. §103(a) as unpatentable over Karim et al., AAPS Annual Meeting Contributed Papers Abstracts, 1997 ("AAPS") in view of Black, EP 0 863 134 ("Black") or Plachetka, U.S. 6,586,458 ("Plachetka") or Block et al., U.S. 6,440,967 ("Block"), and under §103(a) as unpatentable over AAPS in view of Black and Zhang et al., U.S. 5,543,099 ("Zhang"). Claim 3 stands objected to as being dependent upon a rejected base claim.

Reconsideration is respectfully requested of the rejection of claims 1, 2, 4-10, 12-50, 72-75, 84, and 86-90 under §103(a) as unpatentable over AAPS in view of Black or Plachetka or Block and of the rejection of claims 1, 2, 4-10, 12-50, 72-75, 84, and 86-90 under §103(a) as unpatentable over AAPS in view of Black and Zhang.

Claim 1 is directed to a pharmaceutical composition comprising one or more discrete solid orally deliverable dose units, each comprising particulate celecoxib in an amount of about 10 mg to about 1000 mg in intimate mixture with one or more pharmaceutically acceptable

excipients, and having a distribution of celecoxib particle sizes such that D_{90} of the particles is less than 200 μm ; said composition exhibiting upon oral administration a relative bioavailability not less than about 50% by comparison with an orally delivered solution containing celecoxib at the same dosage rate.

AAPS is a short abstract of a scientific paper relating to the disposition kinetics and biotransformation of celecoxib (referred to in the abstract as "SC-58635") in man. AAPS states the following:

"Subjects received a single oral 300 mg dose of [^{14}C]-SC-58635 (100 μCi) as a fine suspension followed by 300 mg of SC-58635 as a capsule after a 15-day washout period. ... Total [^{14}C] and unchanged SC-58635 were readily absorbed with c_{max} values of 1527 (638) and 1077 (649) ng/mL, respectively. The T_{max} , $t_{1/2}$ and $\text{AUC}_{(0-48)}$ values for SC-58635 were 1.9 (0.6) hours, 15.6 (3.5) hours and 8763 (2274) ng/mL * hours." (emphasis added)

The Office states, on page 3 of the May 17, 2005 Office action and on page 2 of the January 13, 2006 Office action, that "AAPS teaches a celecoxib (COX-2 inhibitor) formulation that exhibits a c_{max} values of 1527 and 1077 ng/mL, and a T_{max} of 1.9 hours." Applicants again respectfully draw the Office's attention to the data shown above, and point out that the c_{max} value of 1077 ng/mL refers to **unchanged** celecoxib, while the c_{max} value of 1527 ng/mL refers to total [^{14}C] – that is, it is **not limited to unchanged celecoxib**.

Black discloses that 2-(3,5-difluorophenyl)-3-(4-(methyl-sulfonyl)phenyl)-2-cyclopenten-1-one is useful as a COX-2 inhibitor. Black further discloses that this compound may be administered orally, topically, parenterally, by inhalation spray or rectally (see page 2, lines 2-4). Various pharmaceutical compositions suitable for several of these routes of administration are described, see, e.g., page 2, line 10 through page 3, line 21. Nowhere does Black describe or suggest celecoxib or compositions comprising celecoxib. Nowhere does Black suggest a composition comprising about 10 mg to about 1000 mg of particulate celecoxib having the particle size distribution as set forth in claim 1, wherein the celecoxib is in intimate mixture with one or more pharmaceutically acceptable excipients, and where the composition has the required relative bioavailability. Indeed, nowhere does Black even describe any composition wherein the size of the particles of the active agent in the formulation is disclosed. Nor does Black describe the bioavailability of such a composition relative to an orally-delivered solution.

Plachetka describes methods of treating headaches by administering a composition containing a 5-HT agonist and a long-acting NSAID. Among Plachetka's preferred long-acting

NSAID's are COX-2 inhibitors. See col. 1, lines 18-22. Plachetka lists examples of COX-2 inhibitors, including celecoxib (see col. 3, line 42 and col. 6, line 65 through col. 7, line 10). Nowhere does Plachetka suggest a composition comprising about 10 mg to about 1000 mg of particulate celecoxib having the particle size distribution as set forth in claim 1, wherein the celecoxib is in intimate mixture with one or more pharmaceutically acceptable excipients, and where the composition has the required relative bioavailability. Certainly, Plachetka does not describe any composition wherein the size of the particles of the active agent in the formulation is disclosed, nor does Plachetka describe the bioavailability of such a composition relative to an orally-delivered solution.

Block describes combinations of a COX-2 inhibitor, NSAID, estrogen, or vitamin E and an inverse agonist of the GABA_A α 5 receptor subtype. Suitable COX-2 inhibitors are disclosed, including celecoxib (see, e.g., col. 6, compound no. SC-58635 and col. 15, lines 12 and 13). Block does not describe or suggest a composition comprising about 10 mg to about 1000 mg of particulate celecoxib having the particle size distribution as set forth in claim 1, wherein the celecoxib is in intimate mixture with one or more pharmaceutically acceptable excipients, and where the composition has the required relative bioavailability. Block doesn't describe any composition wherein the size of the particles of the active agent in the formulation is disclosed, nor does Block describe the bioavailability of such a composition relative to an orally-delivered solution.

Zhang describes a process for manufacturing a sustained release pharmaceutical tablet. The process involves a step of granulating an active agent with inactive ingredients, drying the granules (if necessary), and micronizing the granules. See col. 2, lines 59-63. The micronized granules are from 0.1 to 50 μ m in size, see col. 3, lines 53-55. Unmicronized granules of unspecified size may also be included in the tablets in an unspecified amount, see col. 3, lines 61-64. Zhang's tablets are reported to "have a consistent release profile, good content uniformity, and good bioavailability," see col 3, lines 5-7.

The Office states that "it is well known in pharmaceutical art to micronize the active ingredient, especially those active that is high water-insoluble (see Zhang)," see page 6 of the January 13, 2006 Office action. Applicants respectfully disagree.

Pharmaceutical compounds can be administered to patients by many different routes, for example parenterally, intravenously, topically or rectally, to name but a few. Furthermore, medicaments can be formulated in many different dosage forms, for example liquid or solid

dosage forms such as solutions, suspensions, tablets or capsules. Which route of administration and which dosage form is appropriate for a given pharmaceutical compound depends very much on the properties of that compound. In that respect, every compound, including celecoxib, has its unique set of physical, chemical, and pharmacological properties resulting in unique problems to be solved in developing a pharmaceutical composition which can be manufactured at reasonable cost and which can be administered to patients, in particular, with high bioavailability.

The special properties of celecoxib are discussed at page 2, line 18 through page 3, line 4 of the subject application. In particular, celecoxib has low solubility, unfavorable cohesiveness, low bulk density, low compressibility and a tendency to fuse into a monolithic mass upon compressing even when blended with other substances. These properties do not only make celecoxib difficult to process but, in particular, make it difficult to prepare orally deliverable compositions of that compound for administration to patients with high bioavailability, i.e., such that a sufficient amount of the compound actually administered is absorbed by the body at sufficient speed.

However, there is no information in the prior art which would suggest to the person skilled in the art, for example, that, in order to achieve high bioavailability (as measured relative to an orally delivered solution, as required by claim 1), celecoxib should be formulated as discrete solid orally deliverable dose units, rather than, for instance, a liquid suspension or in the form of suppositories.

The Office suggests that micronizing an active agent is well known in the pharmaceutical arts, and thus concludes that the claimed composition (with celecoxib particles having the defined particle size) is obvious. Applicants respectfully disagree. Pharmaceutical science is replete with examples of compounds which showed promising pharmacokinetic properties, but could not successfully be formulated so as to obtain such a composition. Therefore, given the disadvantageous properties of celecoxib, it could by no means be expected with any degree of certainty that a formulation of celebrex with high bioavailability (measured relative to an orally delivered solution, as required by claim 1) could be prepared and it was by no means obvious to the skilled person what properties (for example, celecoxib particle size) such a formulation should have.

Reduction of particle size is by no means the only possibility to increase bioavailability of a pharmaceutical compound. Alternative strategies would include, for example, the formation of

soluble derivatives, the preparation of solutions and the use of excipients influencing the microenvironmental pH at the site of dissolution. Therefore, starting from celecoxib as such, it follows by no means plainly and logically that this should be formulated as discrete solid orally deliverable dose units and that the celecoxib particle size in these dose units should be reduced in order to arrive at a therapeutically superior pharmaceutical composition of that compound. Nor would it have been obvious that this would be practically feasible in the case of celecoxib.

This is all the more true because reduction of particle size can, in fact, have various adverse effects. This is clearly stated in Wadke et al., *Pharmaceutical dosage forms: tablets*, second edition volume I, chapter 1 "Preformulation testing IV. Particle size, shape and surface area" pages 5-6 (1989) ("Wadke," a copy of which is submitted with the enclosed Supplementary Information Disclosure Statement):

"... very fine materials are difficult to handle [5];

... however, if materials become too fine, then undesirable properties such as electrostatic effects and other surface active properties causing undue stickiness and lack of flowability manifest. ...

Size can also be a factor in stability; fine materials are relatively more open to attack from atmospheric oxygen, heat, light, humidity, and interacting excipients than coarse materials. ...

There are several drawbacks to grinding that may make it inadvisable. Some are of lesser importance. For example, there are material losses when grinding is done. Sometimes a static electricity buildup occurs, making the material difficult to handle. Often, however, this problem, if it exists, may be circumvented by mixing with excipients such as lactose prior to grinding. Reduction of the particle size to too small a dimension often leads to aggregation and an apparent increase in hydrophobicity, possibly lowering the dissolution rate and making handling more troublesome. When materials are ground, they should be monitored not only for changes in the particle size and surface area, but also for any inadvertent polymorphic or chemical transformations. Undue grinding can destroy solvates and thereby change some of the important characteristics of a substance. Some materials can also undergo a chemical reaction."

These statements show that the problems the person skilled in the pharmaceutical arts faces in real life in developing pharmaceutical compositions for administration to patients with high bioavailability are very complex and that a single factor such as particle size cannot be viewed in isolation. In view of disadvantages such those identified by Wadke, particle size reduction cannot be said to be the obvious means for increasing bioavailability. Given that various chemical and physical properties of a drug substance are affected by particle size and

that such effects may well be disadvantageous, the expectation of success with which the skilled person would consider particle size reduction as means for increasing bioavailability – let alone as a means for obtaining the high bioavailability of the composition of the present invention – must be rather low.

Moreover, it must also be taken into consideration in assessing whether the subject-matter of claim 1 is obvious that the increase in bioavailability achieved according to the invention is unexpectedly large as shown by the data of Example 11-2 of the subject application. More specifically, the bioavailability of the composition according to the present invention can be seen to be two to three times as high as the bioavailability of unformulated celecoxib. An increase of bioavailability of that order magnitude is very significant in practical terms. It does not only mean that the actual dose of celecoxib administered can be reduced by a corresponding factor, but also that a much faster onset of action can be achieved. Many compounds tested in pre-formulation studies show much smaller increases in bioavailability upon similar reduction in particle size.

Even if it were assumed, for the sake of argument, that the claimed invention differed from the prior art only in the celecoxib particle size distribution and that the choice of such a particle size distribution was obvious in order to increase bioavailability, it does not follow that the subject-matter of claim 1 is obvious. The reason for this is that there was no obvious reliable method for producing a composition according to claim 1 available to the person skilled in the art from the prior art. Such a method has been disclosed, for the first time, in the description of the present invention. More specifically, it is stated at page 7, lines 12-23 of the subject application:

"It has been discovered that milling the celecoxib in an impact mill, such as a pin mill, prior to mixing the celecoxib with excipients to form a composition of the invention, is not only effective in providing improved bioavailability but is also beneficial in overcoming problems associated with the cohesive nature of celecoxib crystals during such mixing or blending. Celecoxib milled using a pin mill is less cohesive than, and does not agglomerate into secondary aggregates of celecoxib particles during blending as readily as, unmilled celecoxib or celecoxib milled using other types of mills such as fluid energy mills. Reduced agglomeration enables a high degree of blend uniformity, which is of particular importance in formulation of unit dosage forms such as capsules and tablets. This result is particularly unexpected given the utility of fluid energy mills such as air jet mills in preparing other pharmaceutical compounds for formulation."

Thus, given the special disadvantageous properties of celecoxib it is, in fact, only by employing a particular milling technique as disclosed in the aforementioned passage from the patent specification, that the problems associated with the cohesive nature of celecoxib can be overcome, i.e., that a uniformly blended composition with the particle size distribution according to claim 1 may be obtained. This finding is surprising because standard milling techniques are usually adequate for preparing other pharmaceutical compounds for formulation.

Analogous considerations apply equally to the present case. Because the composition according to claim 1 can only be made using special unobvious methods disclosed for the first time in the instant application, the composition is unobvious itself. And since, for the above reasons, the subject-matter of claim 1 is unobvious, the subject-matter of the other claims which depend from or refer to claim 1 is also unobvious.

Applicants respectfully acknowledge the Office's comments regarding claim 3. However, in light of the comments above, Applicants respectfully assert that claim 1 is not obvious, and is patentable, and therefore respectfully request that the objection to claim 3 be withdrawn.

Applicants submit that the present invention is now in condition for allowance. Early allowance of all pending claims is respectfully solicited.

Respectfully submitted,



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